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Synthesis of monosaccharide units using fluorous method

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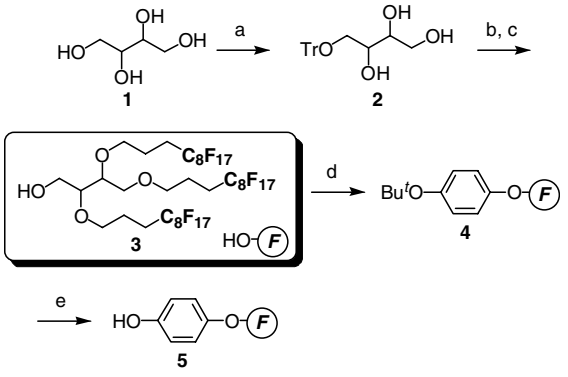
Abstract—The efficient synthesis of monosaccharide units, glycosyl acceptor, and donor, by using the fluorous tag method was achieved. Fluorous tag **5** was stable in each reaction condition to the preparation of various monosaccharide units. Each fluorous synthetic intermediate could be obtained in a straightforward manner by a simple fluorous–organic solvent partition.

Oligosaccharides on cell surfaces play crucial roles in various cellular recognition events, including signal transduction.[1] However, a major obstacle to advances in glycobiology is the lack of pure, structurally well-defined carbohydrates and glycoconjugates. In nature, these compounds are often found in low concentrations and in microheterogeneous forms; this greatly complicates their isolation and characterization. In general, pure, structurally well-defined oligosaccharides are obtained by chemical synthesis, and efficient synthesis has been reported.[2] Recently, we reported the rapid synthesis of oligosaccharides[3] and peptides[4] through the use of various fluorous tags. Fluorous chemistry using a fluorous biphase system was first reported by Horváth and Rábai.[5] In addition, Curran et al.[6] suggested fluorous synthesis (the fluorous tag method) as a strategic alternative to solid-phase synthesis. However, efficiency in oligosaccharide synthesis is limited to the glycosylation step. Monosaccharide units such as glycosyl donors and acceptors are still prepared by classical organic synthesis, requiring many steps and much labor. This has been one of the major and most intractable problems in oligosaccharide synthesis.

The efficient synthesis of monosaccharide units is essential for practical oligosaccharide synthesis. Here we describe the efficient synthesis of two monosaccharides, the glycosyl acceptor, and donor, by using the fluorous tag method.

We considered using the previously reported traditional heavy fluorous tags for monosaccharide unit synthesis. However, those tags include many amide bonds, which pose some risks under standard conditions for protecting group manipulation. For example, the amide bonds are cleaved in the presence of strong bases such as NaOH and NaH, which are commonly used in the synthesis of monosaccharide units. Additionally, detailed analysis of the coupling constant by NMR is made difficult because of the influence of the amide bonds.[3c] Therefore, we designed and synthesized fluorous tag **5** (Scheme 1) to prepare monosaccharide units by the fluorous method.

A triphenylmethyl group was introduced to a primary alcohol of *meso*-erythritol[7] (**1**) to give **2**. Compound **2** was coupled with fluorous tosylate[8] using 15-Crown-5, then the triphenylmethyl group was removed with



Scheme 1. Preparation of fluorous tag **5**. Reaction conditions: (a) TrCl, DMAP, pyridine–DMF, rt 20 h, 51%; (b) NaH, $TsO(CH_2)_3C_8F_{17}$,[8] 15-Crown-5, DMF, rt 19 h; (c) CSA, MeOH–$CHCl_3$, rt 2 h, two steps 70% from 2; (d) 4-*tert*-butoxyphenol, DEAD, PPh_3, THF, reflux 1 h, 98%; (e) 95% aq TFA, rt 2 h; 97%.

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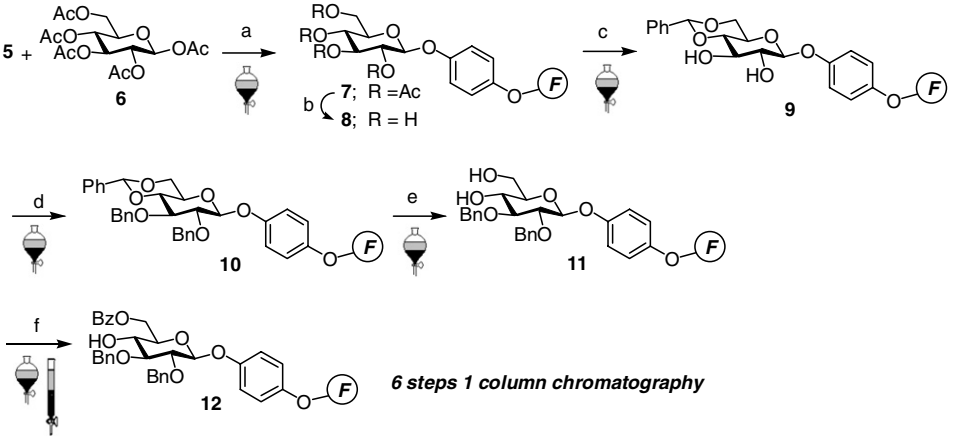
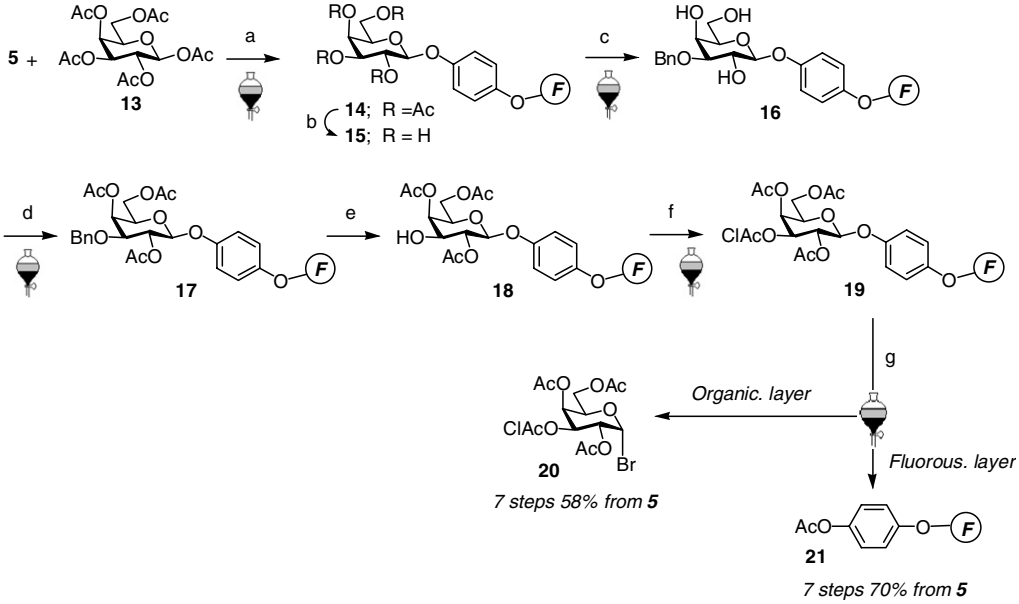
CSA to prepare fluorous tag **3** containing three fluorous chains with a 70% yield. The use of 15-Crown-5 is essential in order to construct three fluorous ether bonds smoothly. 4-*t*-Butoxyphenol was then introduced as a linker by the Mitsunobu reaction to give compound **4** with a 98% yield. Finally, the deprotection of the *t*-butyl group with TFA containing 5% H_2O gave the fluorous tag **5**[9] with 97% yield.

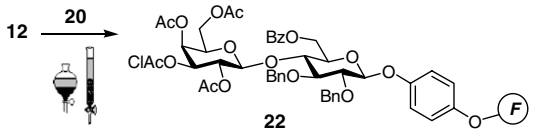
As our model of monosaccharide units, we first selected glycosyl acceptor **12** as shown in Scheme 2. Fluorous tag **5** was attached to per-*O*-acetyl-β-D-glucopyranose[10] (**6**) by $BF_3{\cdot}OEt_2$ as the coupling reagent to give compound **7**. All Ac groups of **7** were removed by transesterification with NaOMe in MeOH–$MeOC_4F_9$[11] to give compound **8**. Treatment of **8** with benzaldehyde dimethylacetal in the presence of CSA gave compound **9**, which was benzylated to give **10**. Cleavage of the benzylidene acetal of **10** by TFA containing 5% H_2O gave diol **11**. The fluorous intermediate **7** and **9**–**11** were each extracted with fluorous mixed solvent[12] ($MeOC_4F_9$–FC72[13] = 4:1) by partitioning the product mixtures between the fluorous mixed solvent and an organic solvent such as 95% aq MeOH or 95% aq MeCN. These compounds, including the fluorous tag, were extracted into the fluorous layer, and the other reagents were extracted into the organic layer.[14] No further purification such as silica-gel column chromatography was conducted. Finally, selective benzoylation to primary alcohol gave crude **12**, which was purified by the fluorous partition step[14] followed by a single silica-gel column chromatography, and then the glycosyl acceptor **12**[15] was obtained with 88% overall yield from the starting material. In Schemes 2–4, the separating funnel symbol indicates that the fluorous partition step was followed by the next step without further purification.



Scheme 2. Synthesis of glycosyl acceptor **12**. Reaction conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2–$MeOC_4F_9$, rt 16 h; (b) NaOMe, MeOH–$MeOC_4F_9$, rt 30 min; (c) $PhCH(OMe)_2$, CSA, MeCN–$MeOC_4F_9$, rt 1 h; (d) BnBr, NaH, 15-Crown-5, THF, rt 20 h; (e) 95% aq TFA, CH_2Cl_2, 0 °C, 1 h; (f) BzCl, Et_3N, CH_2Cl_2–$MeOC_4F_9$, −20 °C, 13 h, then silica-gel column chromatography; 88% from **5**.



Scheme 3. Synthesis of glycosyl donor **20**. Reaction conditions: (a) $BF_3{\cdot}OEt_2$, CH_2Cl_2–$MeOC_4F_9$, rt 17 h; (b) NaOMe, MeOH–$MeOC_4F_9$, rt 30 min; (c) *n*-Bu_2SnO, THF, reflux 4 h, then BnBr, TBAI, reflux 18 h; (d) Ac_2O, Et_3N, DMAP, THF, rt 2.5 h; (e) $Pd(OH)_2$, H_2 gas, EtOAc, rt 1 h; (f) $ClAc_2O$, Pyr, CH_2Cl_2, 0 °C, 1 h; (g) $ZnBr_2$, AcBr, CH_2Cl_2, rt 20 h, then silica-gel column chromatography; 58% from **5**.



Scheme 4. Synthesis of disaccharide **22**. Reaction conditions: AgOTf, $AgClO_3$, CH_2Cl_2, −10 °C, 16 h, 64%.

The column symbols show that each crude product was purified by silica-gel column chromatography.

Next, we describe the synthesis of glycosyl donor **20** by the fluorous method. Coupling of fluorous tag **5** and per-*O*-acetyl-β-D-galactopyranose[10] (**13**) by $BF_3{\cdot}OEt_2$ as described above gave **14**. Compound **14** was exposed to NaOMe in MeOH–$MeOC_4F_9$ to produce **15**. The selective benzylation of **15** using Bu_2SnO gave **16**, which was acetylated to give **17**. The hydrogenation of **17** in the presence of $Pd(OH)_2$ have **18**, followed by monochloroacetylation to give **19**. Fluorous intermediates **14**, **16**, **17**, and **19** could be obtained in a straightforward manner by a simple partition between FC72, or fluorous mixed solvent,[12] and organic solvents.[14] No further purification such as silica-gel column chromatography was carried out.

Finally, cleavage of the fluorous tag using $ZnBr_2$ and AcBr produced crude **20**, which was extracted into the organic layer by partitioning between fluorous mixed solvent ($MeOC_4F_9$–FC72 = 4:1) and 95% aq MeCN. After single silica-gel column chromatography, the glycosyl donor **20**[16] was obtained with 58% overall yield from **5**. Fluorous tag **5** was recovered from the fluorous layer as acetate **21** with 70% yield and was recyclable after deacetylation (Scheme 3).

The glycosyl acceptor **12** and the glycosyl donor **20** were coupled by the Koenigs–Knorr method[17] with AgOTf to give the fluorous disaccharide **22**[14,18] with 64% yield, obtained in only three column chromatographic purification steps from **6** and **13** (Scheme 4).

In conclusion, we achieved the efficient synthesis of monosaccharide units, glycosyl acceptor, and donor, by using the fluorous tag method, with high yield. Fluorous tag **5** was readily introduced to the commercially available monosaccharides **6** and **13**, and the stability in each reaction condition is essential to the preparation of various monosaccharide units. Each fluorous synthetic intermediate could be obtained in a straightforward manner by a simple fluorous–organic solvent partition. As a result, the desired monomeric building blocks were obtained after only one silica-gel column chromatographic purification step. Furthermore, fluorous tag **5** was available to glycosylation. We are currently investigating the possibility of total synthesis of a wide variety of oligosaccharides and glycoconjugates by the fluorous tag method.

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7. *meso*-Erythritol (**1**) was commercially available (Wako Pure Chemical Industries, Ltd).
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9. Compound **5**: ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 6.78$ (d, $J = 8.9$ Hz, 2H), 6.75 (d, $J = 8.9$, 2H), 4.45 (s, 1H), 4.10 (dd, $J = 3.7$, 10.3 Hz, 1H), 3.99 (dd, $J = 4.8$, 10.3 Hz, 1H), 3.74–3.80 (m, 1H), 3.47–3.73 (m, 9H), 2.07–2.24 (m, 6H), 1.79–1.93 (m, 6H). (MALDI-TOF MS.): Calcd for $C_{43}H_{29}F_{51}O_5Na$ *m/z* $[M+Na]^+$: 1617.6; found, 1617.6.
10. Per-*O*-acetyl-β-D-glucopyranose (**6**) and per-*O*-acetyl-β-D-galactopyranose (**13**) were commercially available (TOKYO KASEI KOGYO CO., LTD).
11. $MeOC_4F_9$ is a commercially available fluorocarbon solvent (3M, Tokyo), which is called Novec™ HFE-7100 and miscible in common organic solvents and fluorous solvents.
12. Yu, M. S.; Curran, D. P.; Nagashima, T. *Org. Lett.* **2005**, *7*, 3677. We improved the condition of the partitioning in this reference.
13. FC72 is a commercially available fluorocarbon solvent, which consists of perfluorohexane (C_6F_{14}) isomers and is called Fluorinert™ FC-72.
14. The product mixtures containing the fluorous compounds **7**, **9**, **11**, **12**, **14**, **17**, **19**, and **22** were partitioned between fluorous mixed solvent ($MeOC_4F_9$–FC72 = 4:1) and 95% aq MeCN. Compound **10** was partitioned between fluorous mixed solvent and 95% aq MeOH. Compound **16** was partitioned between FC72 and toluene. None of the fluorous compounds were detected by TLC of the organic layer after three extractions with FC72, which shows that these compounds were quantitatively extracted in the fluorous layer.
15. Compound **12**: ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 8.06$ (d, $J = 7.6$ Hz, 2H), 7.56 (t, $J = 7.6$, 1H), 7.43 (*t*, $J = 7.6$ Hz, 2H), 7.27–7.39 (m, 10H), 7.00 (d, $J = 8.9$ Hz, 2H), 6.75 (d, $J = 9.6$ Hz, 2H), 5.06 (d, $J = 11.0$ Hz, 1H), 4.98 (d, $J = 11.0$ Hz, 1H), 4.91 (d, $J = 7.6$ Hz, 1H), 4.84 (d, $J = 11.0$ Hz, 1H), 4.75 (d, $J = 11.7$ Hz, 1H), 4.58–4.65 (m, 2H), 4.08 (dd, $J = 2.1$, 10.3 Hz, 1H), 3.98 (ddd, $J = 2.1$, 5.1, 10.3 Hz, 1H), 3.75–3.81 (m, 1H), 3.47–3.74 (m, 13H), 2.59 (br s, 1H), 2.09–2.23 (m, 6H), 1.80–1.91 (m, 6H). (MALDI-TOF MS.): Calcd for $C_{70}H_{55}F_{51}O_{11}Na$ *m/z* $[M+Na]^+$: 2064.1; found, 2063.4.

16. Compound **20**: ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 6.70$ (d, $J = 4.1$ Hz, 1H), 5.52 (d, $J = 3.4$, 1H), 5.47 (dd, $J = 3.4$, 10.3 Hz, 1H), 5.10 (dd, $J = 4.1$, 10.3 Hz, 1H), 4.50 (t, $J = 6.9$ Hz, 1H), 4.20 (dd, $J = 6.9$, 11.7 Hz, 1H), 4.13 (dd, $J = 6.9$, 11.7 Hz, 1H), 4.00 (s, 1H), 2.16 (s, 3H), 2.12 (s, 1H), 2.06 (s, 2H). HRMS(ESI-TOF MS.): Calcd for $C_{14}H_{18}BrClO_9Na$ m/z $[M+Na]^+$: 466.9715; found, 466.9687.

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18. Compound **22**: ^{1}H NMR (600 MHz, $CDCl_3$) $\delta = 8.05$ (d, $J = 8.2$ Hz, 2H), 7.59 (t, $J = 7.6$, 1H), 7.46 (t, $J = 7.6$ Hz, 2H), 7.24–7.39 (m, 10H), 6.97 (d, $J = 8.9$ Hz, 2H), 6.71 (d, $J = 8.9$ Hz, 2H), 5.29 (d, $J = 3.4$ Hz, 1H), 5.25 (dd, $J = 8.2$, 10.3 Hz, 1H), 5.00 (d, $J = 11.7$ Hz, 1H), 4.88–4.99 (m, 4H), 4.80 (d, $J = 11.0$ Hz, 1H), 4.71–4.77 (m, 2H), 4.31–4.39 (m, 1H), 4.03–4.08 (m, 1H), 3.90–4.02 (m, 5H), 3.84 (dd, $J = 5.5$, 11.0 Hz, 1H), 3.48–3.80 (m, 14H), 2.06–2.23 (m, 12H), 1.95 (s, 1H), 1.79–1.92 (m, 6H). (MALDI-TOF MS.): Calcd for $C_{84}H_{72}F_{51}O_{20}Na$ m/z $[M+Na]^+$: 2428.8; found, 2429.7.